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### **The ubiquitin-proteasome 26s pathway in liver cell protein turnover: effect of ethanol and drugs.**

**French SW, Mayer RJ, Bardag-Gorce F, Ingelman-Sundberg M, Rouach H, Neve And E, Higashitsuji H.**

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Resources

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This article represents the proceedings of a symposium at the 2000 ISBRA Meeting, Yokohama, Japan. The chairs were Samuel W. French and R. J. Mayer. The presentations were (1) The ubiquitin-proteasome 26s pathway in liver cell protein turnover: Effect of alcohol and drugs, by Samuel W. French and F. Bardag-Gorce; The role of CYP2E1 phosphorylation and degradation pathway in the induction of enzyme, by Magnus Ingelman-Sundberg; (3) Role of proteasome in the proteolysis oxidized proteins in experimental chronic alcoholism, by Helen Rouach; (4) Alcohol proteolysis and liver cancer, by R. J. Mayer; (5) Effect of ethanol feeding on the ATP-ubiquitin-proteasome pathway in the liver cell, by F. Bardag-Gorce; (6) Novel mechanisms and targets for intracellular transport of CYP2E1, by E. Neve; and (7) Gankyrin, an oncoprotein commonly over expressed in hepatoma, by H. Higashitsuji.

PMID: 11391075 [PubMed - in process]

☐ 2: Oncogene 2001 Jan 18;20(3):395-398

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### **Do VHL and HIF-1 mirror p53 and Mdm-2? Degradation-transactivation loops of oncoproteins and tumor suppressors.**

**Blagosklonny MV.**

Medicine Branch, National Cancer Institute, NIH, Bethesda, Maryland, MD 20892 USA.

Recently it has been shown that the VHL tumor suppressor targets the hypoxia-inducible transcription factor (HIF-1) for ubiquitin-dependent degradation by the proteasome. Past mysteries of the p53 tumor suppressor help to solve the present puzzles of the VHL tumor suppressor. Thus, Mdm-2 targets the p53 tumor suppressor for ubiquitin-dependent degradation by the proteasome, but, in addition, the p53 transcription factor induces Mdm-2, thus, establishing a feedback loop. Hypoxia or DNA damage by abrogating binding of HIF-1 with VHL and p53 with Mdm-2, respectively, leads to stabilization and accumulation of transcriptionally active HIF-1 and p53. More detailed analysis depicts the VHL/HIF-1 pair as the p53/mdm-2 pair that has turned upside down, suggesting that VHL may be a HIF-1-inducible gene of the feedback loop. The extended model proposes that an oncoprotein and a tumor suppressor due to transactivation coupled with feedback protein degradation might form functional pairs (Rb/E7, E2F/Rb, E2F/Mdm-2, catenin/APC, p27, cyclin D1, Rb/gankyrin), thus, predicting missing links.

Publication Types:

- Review
- Review, tutorial

PMID: 11313969 [PubMed - indexed for MEDLINE]

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☐ 3: Mol Carcinog 2001 Mar;30(3):138-150

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**Sequential changes in hepatocarcinogenesis induced by diethylnitrosamine plus thioacetamide in Fischer 344 rats: induction of gankyrin expression in liver fibrosis, pRB degradation in cirrhosis and methylation of p16(INK4A) exon 1 in hepatocellular carcinoma**

**Park TJ, Kim HS, Byun KH, Jang JJ, Lee YS, Lim IK.**

Department of Biochemistry and Molecular Biology, Ajou University School of Medicine, Suwon, Korea.

To clarify the sequential changes in pRB and p16 during different stages of hepatocarcinogenesis such as fibrosis, cirrhosis, hepatocellular adenoma (HCA), and hepatocellular carcinoma (HCC), male Fischer 344 rats were singly injected with diethylnitrosamine (DEN), immediately followed with phenobarbital for 1 wk and then thioacetamide (TAA) for 39 wk in drinking water. Rats were killed at 9, 20, 30, and 40 wk after DEN initiation and changes of pRB level, p16 gene hypermethylation and in vivo gankyrin expression were examined. Histologic examination showed stepwise appearances of fibrosis, cirrhosis, HCA, and HCC at weeks 9, 20, 30, and 40, respectively. Hypermethylation of p16 exon 1 was not found until HCA but appeared in 50% of the rats with HCC accompanied by complete loss of its mRNA expression.

The amount of glutathione S-transferase--gankyrin bound to pRB and pRB degradation in the liver depended on the concentration of gankyrin and incubation time. Gankyrin expression preceded pRB degradation in liver cirrhosis. In conclusion, gankyrin expression induced in liver fibrosis accelerated the degradation of pRB during liver cirrhosis, and inactivation of p16 exon 1 by DNA hypermethylation occurred during the progression of tumor cells to poorly differentiated HCC. Inactivation of pRB and/or p16 resulted in complete loss of regulation in the cell-division cycle during early and late stages, respectively, of hepatocarcinogenesis. *Mol. Carcinog.* 30:138--150, 2001. Copyright 2001 Wiley-Liss, Inc.

PMID: 11301474 [PubMed - indexed for MEDLINE]

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☐ 4: Nat Med 2000 Jan;6(1):96-99

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**Reduced stability of retinoblastoma protein by gankyrin, an oncogenic ankyrin-repeat protein overexpressed in hepatomas.**

**Higashitsuji H, Itoh K, Nagao T, Dawson S, Nonoguchi K, Kido T, Mayer RJ, Arii S, Fujita J.**

Department of Clinical Molecular Biology, Faculty of Medicine, Kyoto University Shogoin Kawaharacho, Sakyo-ku, Kyoto, 606-8507, Japan.

Hepatocellular carcinoma (HCC) is one of the most common cancers in Asia and Africa, where hepatitis virus infection and exposure to specific liver carcinogens are prevalent. Although inactivation of some tumor suppressor genes such as p53 and p16INK4A has been identified, no known oncogene is commonly activated in hepatocellular carcinomas. Here we have isolated genes overexpressed in hepatocellular carcinomas by cDNA subtractive hybridization, and identified an oncoprotein consisting of six ankyrin repeats (gankyrin). The expression of gankyrin was increased in all 34 hepatocellular carcinomas studied. Gankyrin induced anchorage-independent growth and tumorigenicity in NIH/3T3 cells. Gankyrin binds to the product of the retinoblastoma gene (RB1), increasing its phosphorylation and releasing the activity of the transcription factor E2F-1. Gankyrin accelerated the degradation of RB1 in vitro and in vivo, and was identical to or interacted with a subunit of the 26S proteasome. These results demonstrate the importance of ubiquitin-proteasome pathway in the regulation of cell growth and oncogenic transformation, and indicate that gankyrin overexpression contributes to hepatocarcinogenesis by destabilizing RB1.

PMID: 10613832 [PubMed - indexed for MEDLINE]

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